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Review

Free light chains: Eclectic multipurpose biomarker

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ABSTRACT

The production of antibodies is accompanied by a slight excess of synthesis of κ and λ immunoglobulin light chains; small amounts of them are released in the peripheral blood and can also be found in various body fluids, such as synovial fluid, cerebrospinal fluid, urine and saliva. They are rapidly filtered by the glomerulus and > 99% are reabsorbed from the cells of the proximal convoluted tubule, making them present in the urine in only trace amounts. The production of an excess of protein without a reason or a specific function in a biological system is rare. Free light chains, considered for years a waste product of Ig synthesis, are currently known to be very active molecules, able to bind antigens as well as whole immunoglobulin and helping to develop specific antibody affinity. The ability of free light chains to activate mast cells and then become an active part of the pathogenic mechanisms of chronic inflammatory diseases has increased interest in their clinical use, both as an attractive therapeutic target or as a biochemical marker of disease evolution or remission.

This is an overview of relevant scientific interest that immunoglobulin light chains κ and λ have attracted over the years, a report on the progress in knowledge about their structure and function, with a special focus on their biological meaning and potential clinical utility in different diseases.

1. Introduction

Immunoglobulin (Ig) free light chains κ and λ (FLCs) have always been the subject of great scientific interest, and the progress in knowledge about their structure and function have characterized the history of medicine, beginning with Henry Bence Jones (Bence, 1847), Paul Ehrlich (Ehrlich, 1900) and Arne W. Tiselius (Tiselius and Kabat, 1939), who won the Nobel prize in 1948. These early frontrunners were followed by Frank W. Putnam and Ingemar Berggård, who sought the physico-chemical and structural characteristics of FLCs (Putnam and Hardy, 1955; Berggård and Peterson, 1969). The FLC molecular definition is attributable to Gerald M. Edelman (Edelman and Gaily, 1962) and Rodney R. Porter (Porter, 1973). The numerous experimental studies of Alan Solomon (Solomon, 1976) and Karsten Sølling (Sølling and Sølling, 1979) have also played a fundamental role in describing these proteins.

The development of FLCs assays began in the early 1960s and for over 30 years there have been rudimentary semi-quantitative methods, such as simple and radial immunodiffusion (Mancini method) (Mancini et al., 1965), quantitative methods easily practicable but with poor reproducibility, such as the first radio-immunoassays (SøIling, 1975) which were subsequently made more reliable (Robinson et al., 1982), up to the development of non-radioisotope immunological methods, such as immunoassays (Brouwer et al., 1985), turbidimetric (Tillyer et al., 1991). These assays were not considered able to truly determine FLCs, but probably were measuring total (free and bound) light chains. In 2001 an assay for determining plasma FLCs was found, characterized by the use of specific polyclonal antibodies able to selectively bind to the free chains (Bradwell et al., 2001). This technique was subsequently progressively improved (Briand et al., 2010).

Afterwards, a nephelometric assay using a mixture of monoclonal antibodies (Levinson, 1992; Te Velthuis et al., 2011; Pretorius et al.,

Abbreviations: pFLCs, polyclonal free light chains; IMWG, International Myeloma Working Group; SMM, smoldering multiple myeloma; mFLCs, monoclonal FLCs; CSF, cerebrum-spinal fluid; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Anti-Ro/SSA, Anti-Sjögren's-syndrome-related antigen A; SS-B/La, (anti-Sjögren's syndrome type B); SS, Sjögren syndrome; RTX, Rituximab; anti-dsDNA, anti-double strand DNA; HCV, hepatitis C virus; IPF, idiopathic pulmonary fibrosis; HP, chronic hypersensitivity pneumonitis; BAL, bronchoalveolar lavage; HIV, human immunodeficiency virus; NHL, non-Hodgkin's lymphoma; MC, mixed cryoglobulinemia; IL-10, interleukin 10; EBV, Epstein-Barr virus; MS, Multiple sclerosis; CNS, central nervous system; OB, Oligoclonal immunoglobulins bands; cFLCs, combined polyclonal FLCs; CKD, Chronic Kidney Disease; Ig, Immunoglobulin

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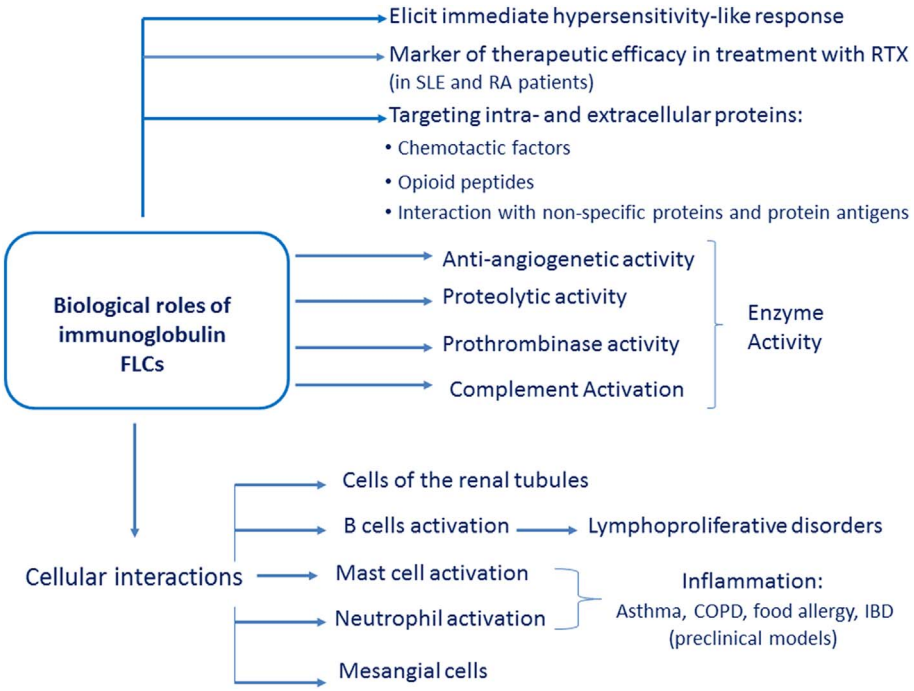

Fig. 1. Biological roles of pFLCs.

2012), multiplex platforms (Campbell et al., 2016) and finally the most recent mass spectrometry (VanDuijn et al., 2015) were applied to FLCs determination. For the first time the International Myeloma Working Group (IMWG) incorporated the FLCs measurement in the 2009 guidelines (Dispenzieri et al., 2009). Since then, numerous guidelines have demonstrated the importance of the FLC assay in the evaluation and monitoring of therapy outcomes, assessment of the prognosis of diseases caused by immunoglobulin deposition and of immune-proliferative disorders (Charafeddine et al., 2012; Graziani and Merlini, 2014). Recently, the IMWG guidelines have highlighted the importance of using an appropriate test for the correct interpretation of the κ/λ ratio in defining different degrees of smoldering multiple myeloma (SMM) (Rajkumar et al., 2014).

The different forms of molecular aggregation of FLCs, such as monomers, dimers, tetramers, and other polymeric forms (Sølling, 1976), their monoclonal polymorphism, arising from the proliferation of different plasma cell clones, make it difficult to achieve an adequate accurancy for these measurements (Jacobs et al., 2016).

The correlation between two different assays is better for κ than λ FLC. The two assays are not entirely equivalent. Care should be taken by interpreting physicians and laboratories when considering switching assays (Cigliana et al., 2017).

Until a few years ago, the interest in FLC measurement was confined to the measurement of monoclonal FLCs (mFLCs) for the management of patients with a monoclonal component. The present contribution is dedicated to polyclonal FLCs (pFLCs) and their measurement as a new biomarker for monitoring diseases and treatment of pathologies different from plasma cell dyscrasia.

2. Expression of pFLCs in the immune response

Early studies on antibody production, typical of the acquired immune response, showed a slight excess by synthesis of immunoglobulin light chains, giving rise to a release of about 500 mg/day of pFLCs in the peripheral blood (Boivin et al., 2004). pFLCs can also be found in various body fluids, such as synovial fluid, cerebrospinal fluid (CSF), urine and saliva.

pFLCs are rapidly filtered by the glomerulus and > 99% are reabsorbed from the cells of the proximal convoluted tubule, making them present in the urine in only trace amounts. The production of an excess of protein without a reason or a specific function in a biological system is rare; FLCs should therefore be considered bioactive molecules rather than a secondary product of the synthesis of immunoglobulins (Ig) without any functional relevance. Numerous studies have elucidated the biological role of pFLCs, in the following main functions: enzymatic (including anti-angiogenic activities), κ light chain is the first molecule associated with the anti-angiogenic activity of Neovastat, an anti-angiogenic extract from shark cartilage (Boivin et al., 2004); proteolytic, pFLCs displayed hydrolytic activity against inactivated vasoactive intestinal peptide (Sun et al., 1994; Paul et al., 1995); prothrombinase activities, conversion of fibrinogen to fibrin was accelerated by the prothrombin fragments generated by the light chain. These finding suggested a novel mechanism whereby antibodies can induce a pro-coagulant state (Thiagarajan et al., 2000); complement activation, in vitro the λ light chain dimer efficiently activates the alternative pathway of complement and represents the first described pathogenic mini-autoantibody in human disease (Jokiranta et al., 1999); specific binding to substrates and enzymes, including protein and non-protein antigens, pFLCs can sensitize mast cells, such that a second encounter with the antigen results in mast-cell activation (Redegeld and Nijkamp, 2003; Van den Beucken et al., 2001); chemotactic factors, X-ray crystallographic techniques showed the binding ways of N-formylated chemotactic peptides to the light chain (Bence-Jones) dimer (Edmundson and Ely, 1985); Enkephalins and beta-casomorphins (opioid peptides) were found to bind in a variety of conformations to a human light chain dimer from a patient with amyloidosis (Edmundson et al., 1987); binding cells, including mast cells, pFLCs have a crucial role in development of contact sensitivity. Although IgE and IgG are central to the induction of immediate hypersensitivity reactions, these results showed that FLC have a similar activity (Redegeld et al., 2002); in renal tubular cells pFLCs endocytosis leads to production of inflammatory cytokines. This may be an important mechanism of chronic tubule-interstitial inflammation process (Sengul et al., 2002). Experimental studies have delineated important aspects regarding the interactions between glomerulopathic pFLCs and mesangial cells, indicating that these interactions are receptor mediated (Teng et al., 2004); in B lymphocytes were defined a new property of pFLCs that inhibits the autonomous signaling ability of the B-cell